



*Effects of a pharmacist-driven comprehensive direct thrombin inhibitor protocol on patient outcomes and medication error rates*

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# Purpose

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- To establish guidelines that ensure the appropriate use, dosing, and monitoring of direct thrombin inhibitors (DTIs)
- To determine the role of a credentialed pharmacist in making decisions regarding dosage adjustments of DTI infusions

# DTI Order Form

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- Clinical practice points
- Initiation of DTI
  - Argatroban
  - Bivalirudin
- Monitoring
  - aPTTs
  - Nurse-driven adjustments
  - Pharmacist-driven adjustments
- Transition to warfarin
- Scoring test for probability of heparin-induced thrombocytopenia (HIT)

# “Pharmacy to Dose”

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- Collaborative drug therapy management policy
- Only credentialed pharmacists may assist the prescriber in managing DTI infusions
- In-hospital versus out-of-hospital
- Documentation

# Objectives

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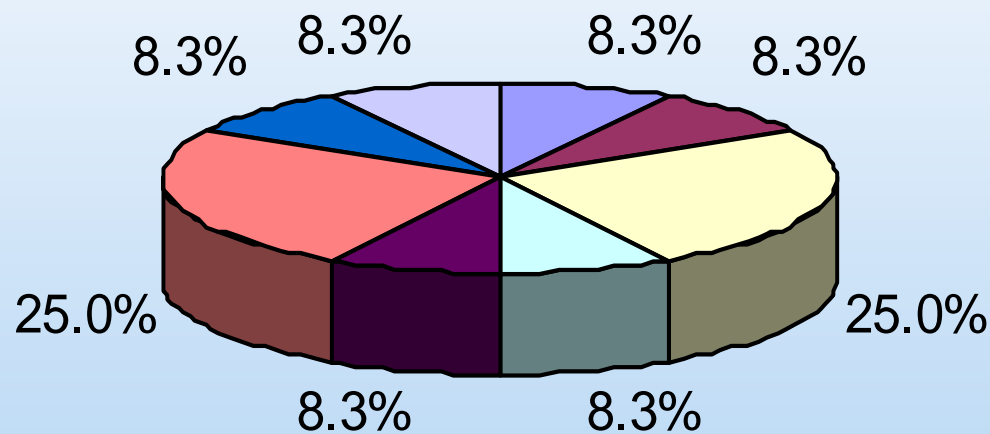
- Primary
  - Time to therapeutic aPTT range
  - Time within therapeutic aPTT range
  - Dosage required to maintain patients within the therapeutic aPTT range
- Secondary
  - Incidence of major and minor bleeding
  - Adherence to the protocol
  - Incidence of medication errors

- Retrospective analysis
- Inclusion criteria
  - All patients who receive argatroban or bivalirudin
  - Suspected HIT
  - $\geq 18$  years of age
- Exclusion criteria
  - Therapy less than 24 hours

# Patient Demographics

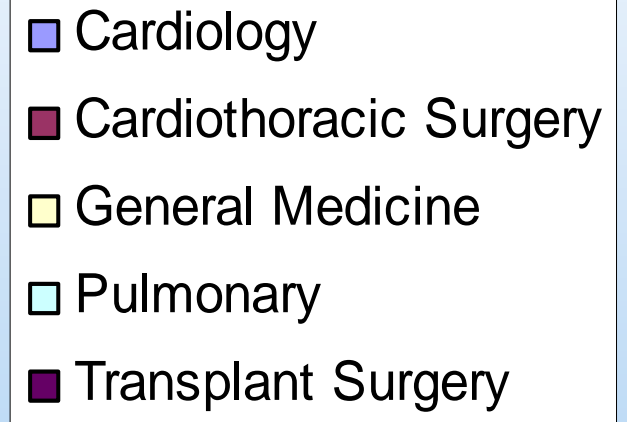
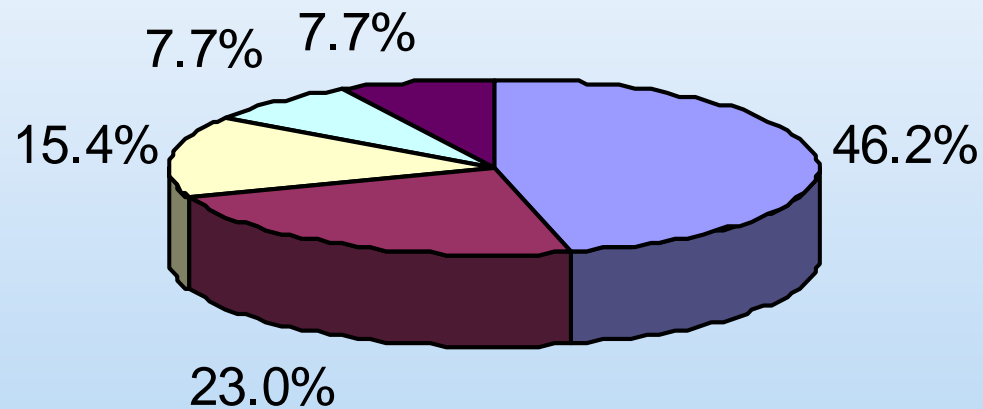
Historical Controls		
	Argatroban n = 12	Bivalirudin n = 13
Age	53 ± 17	61 ± 19
Male	8 (68%)	8 (62%)
Ethnicity		
Caucasian	3 (25%)	11 (85%)
African American	8 (68%)	2 (15%)
Other	1 (8%)	0 (0%)
Comorbidities		
Renal dysfunction	8 (67%)	8 (62%)
Liver dysfunction	2 (17%)	4 (31%)
Recent major surgery	0 (0%)	7 (58%)

# Argatroban Usage By Service



- Cardiology
- Cardiothoracic Surgery
- General Medicine
- General Surgery
- Hematology/Oncology
- Nephrology
- Pulmonary
- Transplant Surgery

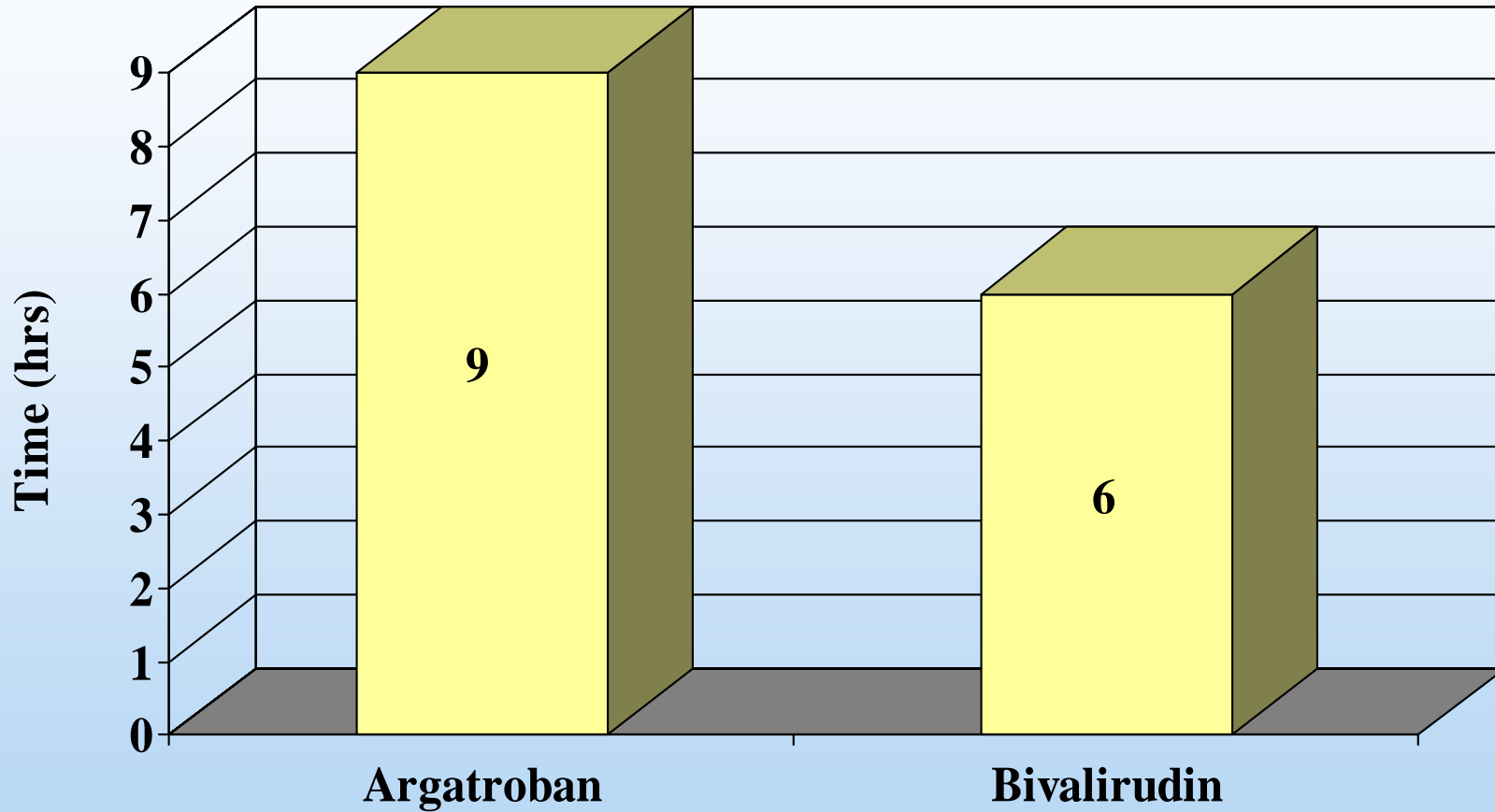
# Bivalirudin Usage by Service



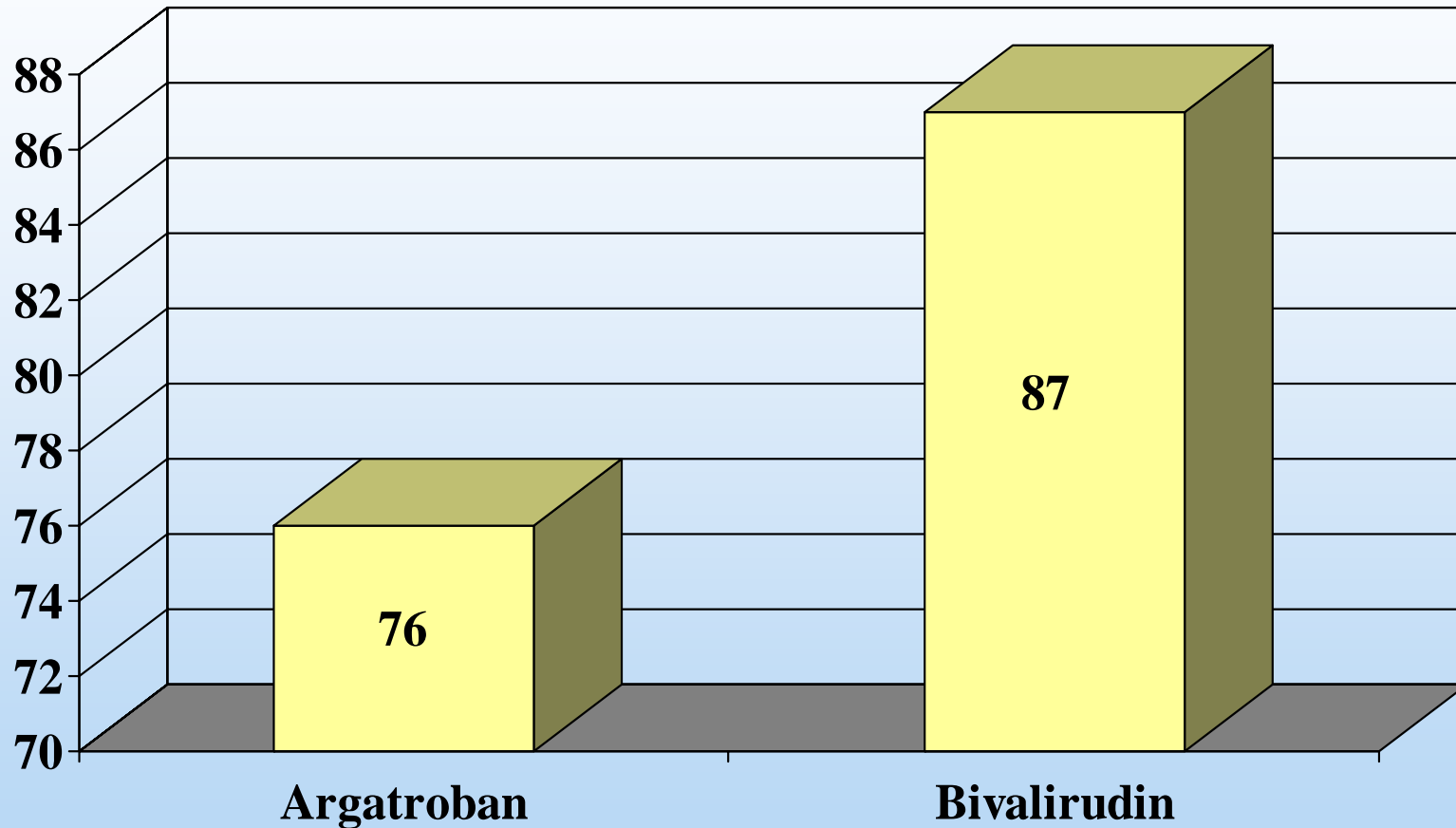
# Historical Controls

	Argatroban n = 12	Bivalirudin n = 13
Length of stay (days)	20 ± 14	27 ± 23
ICU Days	1 ± 2	9 ± 13
Mortality	1 (8%)	4 (31%)
Platelet Factor 4 Positive	5 (42%) 2 (40%)	11 (85%) 6 (55%)
Serotonin Release Assay Positive	4 (33%) 0 (0%)	7 (54%) 1 (14%)
Dialysis CRRT	8 (67%) 1 (8%)	8 (62%) 4 (50%)

# Time to Therapeutic aPTT



# Percentage of Time within Therapeutic Range



# Dosage Required to Maintain Therapeutic aPTTs

	Argatroban	Bivalirudin
Initial Dosage	$2.0 \pm 0.7$ microgram/kg/min	$0.10 \pm 0.07$ mg/kg/hr
Maintenance Dosage	$0.9 \pm 0.7$ microgram/kg/min	$0.13 \pm 0.07$ mg/kg/hr

# Bleeding

	Argatroban n = 12	Bivalirudin n = 13
Baseline hemoglobin	9.4 ± 1.4	10.5 ± 1.6
Lowest hemoglobin	8.2 ± 1.2	9.8 ± 1.7
Transfusions	7 (58%)	3 (23%)
PRBCs	2 units	4 units
FFP	2 units	4 units
Platelets	1.1 units	0.7 units
Documented bleeding	2 (17%)	1 (8%)
Major	1 (50%)	1 (100%)
Minor	1 (50%)	0 (0%)

- Argatroban
  - 7 medication errors reported
    - 57% administration
    - 43% prescribing
- Bivalirudin
  - 3 medication errors reported
    - 100% prescribing

# Conclusions

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- Patients on argatroban or bivalirudin are achieving therapeutic aPTTs after 6 to 9 hours
- Patients on argatroban are only therapeutic about 75% of time on infusion
- Significant bleeding and medication errors are occurring with DTIs
- Standardization of the management of DTI infusions is necessary to optimize patient care

# Limitations

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- No post-implementation patients have been evaluated
- Inherent bias
- Availability of patient information

# Acknowledgements

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- Joseph Mazur, PharmD, BCPS, BCNSP
  - Clinical Pharmacy Specialist, Medical Intensive Care
- David Taber, PharmD, BCPS
  - Clinical Pharmacy Specialist, Transplant Surgery



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# DTI Order Form

**MUSC Health**

**ARGATROBAN & BIVALIRUDIN  
(DTIs) for Heparin Induced Thrombocytopenia  
(HIT) Physician Orders**

Page 1 of 3

Form Origination Date: \_\_\_\_\_ Version Date: \_\_\_\_\_

ALLERGIES/DRUG SENSITIVITY: 1. \_\_\_\_\_ 2. \_\_\_\_\_ 3. \_\_\_\_\_ 4. \_\_\_\_\_

Patient weight: \_\_\_\_\_ kg (calculations are based upon patient's actual weight)

**DIAGNOSIS OF Heparin Induces Thrombocytopenia (HIT) – CLINICAL PRACTICE POINT**

- If platelet counts < 150,000/mm<sup>3</sup> or > 50% reduction in platelet count after heparin initiation
- Review history, labs, and radiographic studies for potential thrombosis sites, determine pretest probability (see page 3) and determination of clinical suspicion.

**High Suspicion** → New thrombosis (suspected or confirmed) OR thrombocytopenia started 4 - 10 days after heparin initiated (but possibly earlier, if exposed to heparin in past 3 - 4 months) AND all other causes of thrombocytopenia ruled-out

**Low Suspicion** → all other situations

- 1. Obtain platelet factor 4 antibody (see table), then if needed,
- 2. Obtain Serotonin Release Assay (SRA) if indicated (see table)

		Platelet Factor 4 Antibody	
		Positive	Negative
Clinical Suspicion	High	<b>HIT confirmed:</b> • Stop heparin & LMWH products • Start DTI	<b>HIT possible, send SRA:</b> • Stop heparin & LMWH products • Consider other causes of thrombocytopenia • Use of DTI specific to patient risk vs. benefit
	Low	<b>HIT possible, send SRA:</b> • Stop heparin & LMWH products • Consider other causes of thrombocytopenia • Use of DTI specific to patient risk vs. benefit	<b>HIT unlikely:</b> • Consider restart heparin or LMWH if needed • Use of DTI probably not necessary

DTI – direct thrombin inhibitor      LMWH – low molecular weight heparin

This form may be completed on line. Tab or move cursor to text field and type in text.

For HIPAA Compliance reasons, this form IS NOT TO BE SAVED with patient information. Selecting the PRINT button will clear all information from the note.

Patient Name \_\_\_\_\_  
MRN \_\_\_\_\_

**PATIENT IDENTIFICATION LABEL**

**1. DISCONTINUE ALL HEPARIN PRODUCTS (Including flushes and LMWH products)**

**2. INDICATION** for DTI use:  
 Anticoagulation for prophylaxis / treatment of thrombosis in patients with suspected HIT  
 Anticoagulation for prophylaxis / treatment of thrombosis in patients refractory or allergic to heparin

**Clinical Practice Point – Bivalirudin is the preferred DTI in patients with hepatic insufficiency AND Argatroban is preferred in patients with renal insufficiency**

**3. ORDER:**  STAT OR  Begin at (time and date) \_\_\_\_\_

**PHARMACY TO DOSE**

**ARGATROBAN** 250 mg/250 mL at \_\_\_\_\_ micrograms/kg/min (usual dose is 2 micrograms/kg/min).  
Hourly dose = \_\_\_\_\_ mg/hr = \_\_\_\_\_ mL/hr

**BIVALIRUDIN** 250 mg/250 mL at \_\_\_\_\_ mg/kg/hour (usual dose for patient with normal renal function is 0.2 mg/kg/hour).  
Hourly dose = \_\_\_\_\_ mg/hr = \_\_\_\_\_ mL/hr

Bivalirudin dosing with renal impairment (**CrCl < 59 mL/min**)

CrCl 30-59 mL/min: 0.16 mg/kg/hr (= \_\_\_\_\_ mg/hr). Infusion rate = \_\_\_\_\_ mL/hr

CrCl 10-29 mL/min: 0.08 mg/kg/hr (= \_\_\_\_\_ mg/hr). Infusion rate = \_\_\_\_\_ mL/hr

CrCl <10 mL/min (off dialysis) 0.02 mg/kg/hr (= \_\_\_\_\_ mg/hr). Infusion rate = \_\_\_\_\_ mL/hr

CVVH dosing: 0.05 mg/kg/hr (= \_\_\_\_\_ mg/hr). Infusion rate = \_\_\_\_\_ mL/hr

Physician Signature \_\_\_\_\_ Pager ID \_\_\_\_\_ Date \_\_\_\_\_ Time \_\_\_\_\_ AM/PM

How to Diagnose HIT –  
Clinical Pearls for  
Prescribers

Which DTI to order  
and how to initiate  
medication...

# Initiation of DTI

## 1. DISCONTINUE ALL HEPARIN PRODUCTS (Including flushes and LMWH products)

## 2. INDICATION for DTI use:

Anticoagulation for prophylaxis / treatment of thrombosis in patients with suspected HIT

Anticoagulation for prophylaxis / treatment of thrombosis in patients refractory or allergic to heparin

*Clinical Practice Point – Bivalirudin is the preferred DTI in patients with hepatic insufficiency AND Argatroban is preferred in patients with renal insufficiency*

## 3. ORDER: STAT OR Begin at (time and date) \_\_\_\_\_

### PHARMACY TO DOSE (RN call pharmacy with questions)

**ARGATROBAN** 250 mg/250 mL at \_\_\_\_\_ micrograms/kg/min (usual dose is 2 micrograms/kg/min). Hourly dose = \_\_\_\_\_ mg/hr = \_\_\_\_\_ mL/hr

**BIVALIRUDIN** 250 mg/250 mL at \_\_\_\_\_ mg/kg/hour (usual dose for patient with normal renal function is 0.2 mg/kg/hour). Hourly dose = \_\_\_\_\_ mg/hr = \_\_\_\_\_ mL/hr

### Bivalirudin dosing with renal impairment (**CrCl < 59 mL/min**)

CrCl 30-59 mL/min: 0.16 mg/kg/hr (= \_\_\_\_\_ mg/hr). Infusion rate = \_\_\_\_\_ mL/hr

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CVVH dosing: 0.05 mg/kg/hr (= \_\_\_\_\_ mg/hr). Infusion rate = \_\_\_\_\_ mL/hr

# DTI Order Form

**MUSC Health**

**ARGATROBAN & BIVALIRUDIN  
(DTIs) for Heparin Induced Thrombocytopenia  
(HIT) Physician Orders**

Page 2 of 3

Form Origination Date: \_\_\_\_\_ Version Date: \_\_\_\_\_

ALLERGIES/DRUG SENSITIVITY: 1. \_\_\_\_\_ 2. \_\_\_\_\_ 3. \_\_\_\_\_ 4. \_\_\_\_\_

Patient weight: \_\_\_\_\_ kg (calculations are based upon patient's actual weight)

**4. MONITORING:**

- Check aPTT prior to initiation of infusion
- Check aPTT 2 hours after start of infusion, then
- Check aPTT every 4 hours:
  - If aPTT within range for 2 consecutive aPTTs, go to step 4
  - If aPTT is not within therapeutic range (50 – 80 seconds), use the chart below for dose adjustments
  - Check aPTT 2 hours after any dosage change and then if within range return to checking aPTT every 4 hours
- Check aPTT daily when aPTT falls within therapeutic range for 2 consecutive aPTTs (EXCEPTION: Check aPTT q12 hrs with renal impairment or if renal or liver function declines.)
- All aPTTs should be drawn from the arm not used for the argatroban or bivalirudin infusion
- Maintain anticoagulation monitoring flowsheet
- Adjust argatroban or bivalirudin infusion rate by the following scale:

This form may be completed on line. Tab or move cursor to text field and type in text.

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Patient Name \_\_\_\_\_  
MRN \_\_\_\_\_

PATIENT IDENTIFICATION LABEL

aPTT (sec)	Stop Infusion	Infusion Rate Change	Check next aPTT
< 50		Increase rate by 20%	• 2 hours • If repeat aPTT still < 50 call PharmD to dose
50 – 80		No change in rate	• 4 or 12 hours, or daily (see # 4 Monitoring, step 4 above)
> 80	• Hold infusion for 1 hour, then obtain STAT aPTT* • If STAT aPTT still > 80, call PharmD to dose If aPTT within range (50 – 80 sec), restart at lower infusion rate (i.e., decreasing rate by 50%)	Decrease rate by 50%	2 hours

Physician Signature \_\_\_\_\_ Pager ID \_\_\_\_\_ Date \_\_\_\_\_ Time \_\_\_\_\_ AM/PM  
new

**Clinical Practice Points:**  
**Transition to warfarin (Coumadin®) therapy:**

- Obtain daily platelet count
- Consider transition to warfarin:
  - Platelet count > 100,000/microL
  - Patient on anticoagulation with DTI and is stable
- Overlap warfarin and DTI therapy with a therapeutic PT-INR in the 2-3 range for 2 days
- Argatroban will falsely elevate the INR, please utilize diagram below on page 3 for dosage adjustments

Initiate warfarin therapy using the expected daily dose of warfarin while maintaining infusion of Argatroban. If a loading dose of warfarin should not be used. To avoid gastrointestinal complications, overlap of Argatroban and warfarin is suggested.

How to Monitor the DTI

How to transition to warfarin

# Monitoring of DTIs

## MONITORING:

1. Check aPTT prior to initiation of infusion
2. Check aPTT 2 hours after start of infusion, then
3. Check APTT every 4 hours:
  - If aPTT within range for 2 consecutive aPTTs, go to step 4
  - If aPTT is not within therapeutic range (50 – 80 seconds), use the chart below for dose adjustments
  - Check aPTT 2 hours after any dosage change and then if within range return to checking aPTT every 4 hours
4. Check aPTT daily when aPTT falls within therapeutic range for 2 consecutive aPTTs (EXCEPTION: check aPTT q12hrs with renal impairment or renal or liver function declines)  
(EXCEPTION: Check aPTT q12 hrs with renal impairment or if renal or liver function declines.)
5. All aPTTs should be drawn from the arm not used for the argatroban or bivalirudin infusion
6. Maintain anticoagulation monitoring flowsheet
7. Adjust argatroban or bivalirudin infusion rate by the following scale:

# Monitoring of DTIs

aPTT (sec)	Stop Infusion	Infusion Rate Change	Check next aPTT
< 50		Increase rate by 20%	<ul style="list-style-type: none"> <li>• 2 hours</li> <li>• <b>If repeat aPTT still &lt; 50 call “PharmD to dose” if checked</b></li> </ul>
50 – 80		No change in rate	4 or 12 hours, or daily (see # 4 Monitoring, step 4 above)
> 80	<ul style="list-style-type: none"> <li>• Hold infusion for 1 hour, then obtain STAT aPTT*</li> <li>• <b>*If STAT aPTT still &gt; 80, call the physician or “PharmD to dose” if checked</b></li> <li>• If aPTT within range (50 – 80 sec), restart at lower infusion rate (i.e., decreasing rate by 50%)</li> </ul>	Decrease rate by 50%	2 hours